VETERANS HEALTH ADMINISTRATION
OFFICE OF PATIENT CARE SERVICES
TECHNOLOGY ASSESSMENT PROGRAM

BRIEF OVERVIEW:

SYSTEMATIC REVIEWS FOR
AMYOTROPHIC LATERAL SCLEROSIS

Prepared by
Karen Flynn, DDS, MS

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TECHNOLOGY ASSESSMENT PROGRAM

An Effective Resource for Evidence-based Managers

VA's Technology Assessment Program (TAP) is a national program within the Office of Patient Care Services dedicated to advancing evidence-based decision making in VA. TAP responds to the information needs of senior VA policy makers by carrying out systematic reviews of the medical literature on health care technologies to determine "what works" in health care. "Technologies" may be devices, drugs, procedures, and organizational and supportive systems used in health care. TAP reports can be used to support better resource management.

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- The ***Outline and Bibliography*** provide structured support to client groups planning to conduct their own evidence reviews.

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VA Technology Assessment Program • Office of Patient Care Services
Boston VA Healthcare System (11T) • 150 S. Huntington Ave. • Boston, MA 02130
Tel. (857) 364-4469 • Fax (857) 364-6587 • VATAP@va.gov

A SUMMARY FOR HTA REPORTS
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VATAP is a member of the International Network of Agencies for Health Technology Assessment (INAHTA) [www.inahta.org]. INAHTA developed this checklist© as a quality assurance guide to foster consistency and transparency in the health technology assessment (HTA) process. VATAP will add this checklist© to its reports produced since 2002.

This summary form is intended as an aid for those who want to record the extent to which a HTA report meets the 17 questions presented in the checklist. It is NOT intended as a scorecard to rate the standard of HTA reports – reports may be valid and useful without meeting all of the criteria that have been listed.

Brief Overview:
Systematic Reviews for ALS
June 2009

Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?	√		
4. Statement on whether report externally reviewed?		√	
5. Short summary in non-technical language?			√
Why?			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?	√		
How?			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
What?			
12. Results of assessment clearly presented?	√		
13. Interpretation of the assessment results included?	√		
What Then?			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?			√
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

CONTRIBUTORS TO THIS REVIEW: **no conflicts of interest reported**

TAP staff person/position	Role	Tasks
Karen Flynn Program Manager Boston	Primary author	Conception and conduct of review: • Communication with client; • Interim information; • Analytic framework; • Draft review; • Final review.
Elizabeth Adams Health System Specialist Boston	Consultation throughout project	Internal content and format review of draft.
Elaine Alligood Information Specialist Boston	Literature database searches	Database searches: • Design strategy; • Choose/manage databases; • Strategy text and bibliography for report.
Bernard Spence Administrative Officer Boston	Administrative support	• Budget/resources; • Project tracking.
Sarah Curran Library Technician Boston	Article retrieval	Information retrieval: • Full text from print journals and electronic resources; • Manage reference lists.
Valerie Lawrence Physician Advisor San Antonio	Content and methods review	Final review: • Internal consistency, • Clarity; • Clinical context; • Methods.

ABBREVIATIONS IN THIS REVIEW

AALSRS,	Appel Amyotrophic Lateral Sclerosis Rating Scale
AAN,	American Academy of Neurology
ALS	Amyotrophic Lateral Sclerosis
ALSFRS,	ALS Functional Rating Scale
BMI,	body mass index
CCOHTA,	Canadian Coordinating Office for Health Technology Assessment
CI,	95% confidence interval
CNS,	central nervous system
CNTF,	ciliary neurotrophic factor
COPD,	chronic obstructive pulmonary disease
EB,	evidence-based
EFNS,	European Federation of Neurological Societies
ELISA,	enzyme linked immuno-sorbent assay
EMG,	electro-myograph or -myographic
fALS,	familial ALS
FVC,	forced vital capacity
INAHTA,	International Network of Agencies for Health Technology Assessment
LMN,	lower motor neuron
LOS,	Length of stay
MD,	multi-disciplinary
MND,	motor neuron disease
MS,	multiple sclerosis
NEALS,	northeastern ALS clinical trials consortium
NHS,	National Health System (UK)
NICE	National Institute for Clinical Excellence (UK)
NIV,	non-invasive ventilation
NIPPV,	non-invasive positive pressure ventilation
NS,	not statistically significant
OHRC,	Oregon Health Resources Commission
OPCS,	Office of Patient Care Services
PARALS,	Piedmonte and Valle d'Aosta Register for ALS
PWL,	percent weight loss
RCT,	randomized controlled trial
rhIGF-I	recombinant human insulin-like growth factor I
RR,	relative risk
sALS,	sporadic ALS
SCI,	spinal cord injury
SF-36,	Short form health survey
SLA,	sclérose latérale amyotrophique
SMD,	standardized mean difference
TV,	tracheostomy ventilation
QALY,	quality-adjusted life year
QoL,	quality of life
UMN,	upper motor neuron
VAS,	visual analog scale
VEGF,	vascular endothelial growth factor

BRIEF OVERVIEW:
Systematic Reviews For
Amyotrophic Lateral Sclerosis

CONTEXT

VHA's OPCS asked TAP for a review of the literature as support for The National Task Group for Development of an Integrated System of Care for Veterans with Amyotrophic Lateral Sclerosis (ALS). Areas of particular interest were treatment and organization of care. The broad charge mandated an overview of available systematic reviews, guidelines based on such reviews, and economic evaluations using high quality primary studies or reviews as sources of effectiveness data. This document will refer collectively to these publication types as "reviews".

As explained in greater detail below, a catalog of reviews provides an immediately accessible "snapshot" of the state of the research literature by highlighting those research questions for which a quantity sufficient to warrant review effort, and presumably quality of research, has been published. Such a catalog also synthesizes a larger body of literature than otherwise would be feasible for any single review, while defining gaps in the knowledge base for a research agenda. Reviewers may find insufficient quantity or quality of published research to definitively answer their questions, but rigorous methods make even apparently negative findings valuable to understanding the knowledge base.

TAP used a catalog of reviews to determine which research questions would yield a sufficient quality and quantity of literature to warrant a review effort. A catalog of reviews (detailed below) is a useful tool because it synthesizes a larger body of literature than would be possible in any single review, thus identifying bodies of literature as well as gaps in the literature base.

BACKGROUND

> *"Amyotrophic lateral sclerosis (ALS) is a progressive and nearly always fatal disease that affects a person's nervous system. It is sometimes referred to as Lou Gehrig's disease, after the famous baseball player who died from it. When a person develops ALS, nerve cells in the brain and spinal cord degenerate…*
>
> *ALS affects 20,000-30,000 men and women in the United States. It occurs in people of all races and ethnic backgrounds. About 5-10% of ALS cases are inherited; the cause of the remaining 90-95% of cases is not known. Four recent epidemiologic studies have reported an association between ALS and prior service in the US military. Three of those studies evaluated veterans of the 1991 Persian Gulf War; the fourth evaluated veterans who served in the military in the period 1910-1982."* National Academy of Sciences (2006).

> *"…unexplained large differences in clinical presentation (initial symptoms may be spinal or bulbar in nature), age of onset (ranging from juvenile to the very elderly) and survival time (from a few months to more than 20 years). Elucidating the modifying factors has important consequences for our understanding of neuron degeneration and development of therapy.*
>
> *Five types of familial ALS (fALS) have been assigned to loci of the human genome. ALS1, an autosomal dominant form of adult ALS affecting 21-23% of individuals with fALS, is associated with more than 100 mutations in the gene encoding Cu/Zn superoxide dismutase (SOD1).."* Lambrechts (2003).

> *"Despite the large number of studies on the natural history of amyotrophic lateral sclerosis (ALS), most of the data have been based on large clinical series enrolled at ALS referral centers; these are selected groups of patients and the collection of data is largely retrospective. Recent population based series based on the presence of registries in a defined geographical area have shown a broader range of clinical phenotypes and have prospective collection of information both*

on prognostic indicators and outcome; findings from these studies are likely to be more representative of the entire clinical spectrum of the disease. Most of the studies have been conducted before the introduction of standardized criteria for diagnosis of ALS (El Escorial and Airlie House Criteria) and it is still not clear if El Escorial categories have any prognostic value." Zuccolella (2008).

"Amyotrophic lateral sclerosis (ALS) affects people of all ages, but whether the wide range of age at onset is due to distinct diseases or merely reflects phenotypic variability of the same disorder is unknown...young-adult amyotrophic lateral sclerosis with the predominant upper motor neuron phenotype represents a distinctive clinical variant characterized by a unique clinical pattern, longer survival, and male prevalence." Sabatelli (2008).

"The term motor neuron disease (MND) is sometimes used synonymously with ALS, but may also be used as a more encompassing term that includes progressive bulbar palsy, progressive muscular atrophy, and primary lateral sclerosis…" Benatar (2009).

"While the aetiology of MND is unknown, current evidence suggests that multiple interacting factors contribute to motor neuron injury in MND. The working hypothesis is that MND, like many other chronic diseases, is a complex genetic condition, and the relative contributions of individual environmental and genetic factors are likely to be small. The three key pathogenetic hypotheses are genetic factors, oxidative stress, and glutamatergic toxicity, which result in damage to critical target proteins such as neuro-filaments and organelles such as mitochondria.

The burden of disease and economic impact of MND upon patients, their caregivers (often family members) and society are substantial, often beginning long before the actual diagnosis is made, and increasing with accumulating disability and the need for medical equipment and assisted care. At present, the only drug approved in the USA, Australia, and many European countries, for treatment of MND is riluzole, which is thought to prolong median survival by about two or three months.." Ng (2008).

"The classification and terminology used to describe the different motor neuron diseases is not always clear or consistent. This confusion partly reflects our ignorance of the underlying causes and mechanism of neuronal damage. There is also debate as to the extent to which different syndromes are simply manifestations of the same disease process, and, indeed, whether there are several different disease mechanisms underlying what phenomenologically appears to be the same disease." Stewart (2001).

"Despite numerous promising research discoveries, amyotrophic lateral sclerosis (ALS) remains a progressive disorder with a grim prognosis. Though the pathogenesis of ALS is still largely unknown, there have been tremendous strides in understanding the heritable forms of ALS and excellent work has been done on excitotoxic and free-radical theories to explain the disease. Translational research has led to numerous clinical trials, many of which are ongoing. There are also many potential therapeutic agents in development. There is also promising research underway in the area of stem cells and delivery of growth factors via viral vectors.

Whilst there is reason to be optimistic about future therapies directed at the underlying causes of ALS, the current reality is that most patients die within 3-5 years of disease onset. The greatest immediate impact on people with ALS will come from improvements in clinical care. Improvements in nutritional approaches, including earlier use of gastrostomy tubes, better communication devices, better mobility assistance, and improvements in respiratory care have undoubtedly resulted in improved quality and quantity of life for individuals with ALS. Additionally, proper attention to palliative care at the end of life will lead to greater comfort for patients and their care providers. Recommendations regarding optimal clinical care have been proposed by several different expert panels…" Lechtzin (2009).

"Whatever the diagnostic limitations experienced with ALS, they become less significant in comparison to the therapeutic limitations. The only approved therapy for ALS exerts a modest benefit. The most dramatic interventions provide symptomatic benefit in the form of improved nutrition through the use of gastrostomy and improved ventilation through the use of BiPap (bi-level intermittent positive pressure) or a respirator. By any standard, ALS patients are one of the

> *few groups that have not materially benefited from the technological advances that have characterized modern medicine…"* Smith (2001).
>
> *"Cost effectiveness has become a major issue. We are clearly entering an age where we will see a number of drugs being introduced with only modest benefit. MY guess is that all of these drugs will initially have about the same effects as what we have already. We are not going to wake up one morning and have a drug that cures the disease, but rather, it will be a prolonged series of steps, probably with combination trials, but with modest increments…Canada has not yet approved the use of riluzole because of the cost of the drug. That government has decided that the benefits of riluzole do not justify the cost."* Munsat (2001).

METHODS

First, TAP identified available systematic reviews for ALS. Systematic reviews (detailed below) qualify as reproducible science. Review production requires a threshold level of available primary research tailored to the review question. Hence, a catalog of published systematic reviews provides an immediately accessible overview of the general status of a body of research literature. Conversely, the lack of published high-quality reviews indicates a corresponding lack of published research on issues of interest to the Task Group.

Then, TAP conducted further searches to determine whether more recent studies had been conducted that would change the review's conclusions. Finally, TAP posted an electronic mail query to INAHTA colleagues, seeking information on organizations for ALS care within member agencies' healthcare systems.

Search strategy/selection criteria

TAP repeatedly searched Medline and the Cochrane Library for systematic reviews, guidelines, meta-analyses, and economic evaluations using the terms "amytrophic lateral sclerosis" or "Lou Gehrig's disease" to identify full-text reviews published in English from 2000 to 2009. These reviews synthesized clinical research (diagnosis, treatment, or organization of ALS care) and involved adult human patients. Searches for subsequently published review-eligible randomized controlled trials (RCTs) were conducted in May, 2009, and all searches were finally updated on June 15, 2009.

TAP excluded:

- Narrative reviews, opinion pieces, and other publications lacking primary clinical data;
- Articles already covered in systematic reviews;
- "Quasi-systematic" reviews, i.e., those indexed or titled as systematic but which on close examination do not fully meet criteria or are inadequately reported to judge. These are noted in Table 2 but not abstracted in detail.

ANALYTIC FRAMEWORK

Systematic reviews

Cook (1997) and Mulrow (1997) define systematic reviews: "*Systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their "subjects". They synthesize the results of multiple primary investigations by using strategies that limit bias and random error…"*

The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews: the latter synthesize articles without reporting methods of selection or quality assessment criteria and thus do not qualify as reproducible unbiased science. Systematic reviews:

- Ask a focused clinical question;
- Conduct a comprehensive search for relevant studies using an explicit search strategy;
- Uniformly apply criteria for inclusion and exclusion of studies;
- Rigorously and critically appraise included studies;
- Provide detailed analyses of the strengths and limitations of included studies.

Systematic reviews can be quantitative (i.e., meta-analytic, applying statistical methods to summarize study results) or qualitative; in either case the inferences or conclusions of the review must follow logically and specifically from the evidence presented. The rigor of this approach is illustrated by the place of systematic reviews in evidence grading schemes (Cook 1995; Guyatt 1995; Sullivan 2005), where they receive the highest level designation. Reviews produced by the Cochrane Collaboration (www.cochrane.org) set the standard for rigor of methods and validity of conclusions. Cochrane reviews are meta-analytic where primary studies permit.

Some reviews classified by their authors or by indexing staff as "systematic" can be less than perfectly conducted and/or reported. Grimshaw (2002) critiques such reviews for:

- Ignoring methodological weaknesses in primary studies, such as unit of analysis errors (analysis of unadjusted patient data when the unit of randomization is the physician), which results in artificially extreme p values and overly narrow confidence intervals;
- Vote-counting methods, which add up the number of positive and negative comparisons and base effectiveness conclusions on the counts. Positive comparison counts fail to provide an estimate of effect size and ignore the precision of the estimates from primary studies, or fail to exclude comparisons with unit of analysis errors.

While recognizing the limitations cited above, a vote count may be the logical response of an otherwise good-quality review to heterogeneity (in research questions, study design, patients, interventions, or outcomes) among primary studies that precludes other methods of synthesis.

TAP includes here less than perfect systematic reviews that were clearly conducted to characterize a body of literature to include all studies that increase our knowledge about management of ALS

RESULTS

Diagnosis

In the absence of systematic reviews on diagnosis of ALS, the quasi-systematic review [Andersen (2005)] prepared for the European Federation of Neurological Societies (EFNS) consensus recommendations provides a comprehensive overview of the diagnosis of ALS (Table 1).

Table 1. Diagnosis of ALS [Adapted from Andersen (2005)]

Clinical criteria		El Escorial revised research criteria (Brooks, 2000)	
Category	**Criteria**	**Category**	**Criteria**
Positive criteria must be present	LMN signs, including EMG features in clinically unaffected muscles	Clinically definite	UMN and LMN signs in three regions
	UMN signs	Clinically definite – laboratory supported	UMN and/or LMN signs in one region *AND* patient is carrier of pathogenic gene mutation
	Progression of signs and symptoms	Clinically probable	UMN and LMN signs in two regions with some UMN signs rostral to LMN signs
Requires absence of/ exclusion criteria	Sensory signs	Clinically probable-laboratory supported	UMN signs in one or more regions *AND* LMN signs defined by EMG in at least two regions
	Sphincter disturbances	Clinically possible	UMN and LMN signs in one region or
	Autonomic features		UMN signs in at least two regions or
	Basal ganglia dysfunction		UMN and LMN signs in two regions with no UMN signs rostral to LMN signs
	Alzheimer-type dementia	Andersen (2005): *"We do not recommend that patients are told they have 'definite, probable or possible' ALS. The clinician must decide, on balance of probability, whether or not the patient has ALS, even in the absence of unequivocal UMN and LMN signs."*	
	ALS 'mimic' syndromes		
Diagnosis of ALS supported by	Fasciculations in one or more regions		
	Neurogenic changes in EMG		
	Normal motor and sensory nerve conduction		
	Absence of conduction block		

Treatment

Eighteen independent reviews of interventions and three related publications identified by TAP searches are outlined in Table 2 below and abstracted in detail in Appendix Table 4. Four of the reviews (Stewart, 2001; NICE, 2001; Bryan, 2001; Tavakoli, 2002) represent stages of work in the process of developing guidance for the National Health System (NHS), with Stewart (2001) providing core evidence on which others based further analyses or policy recommendations.

As detailed in Table 2 and Appendix Table 4, completed high quality reviews cover approximately 160 studies of interventions for ALS from database inceptions in the 1960s to 2007. Table 2, column 2 indicates the very small numbers of studies available to reviewers. No completed systematic reviews address diagnosis or organization of ALS care, although one (Ng, 2008; Appendix Table 4) is planned. Descriptive primary studies relevant to organization of care are abstracted in Appendix Table 5.

The only two subsequently published primary studies (Jackson, 2009; Carratù, 2009) eligible for any Appendix Table 4 review also are abstracted in Table 2. Otherwise, Table 2 reviews represent the most recent available high-quality research on ALS treatment effectiveness.

Quasi-systematic reviews are listed in the table to acknowledge their authors' attempts to conduct reviews systematically and as an indication of a body of published literature, but are not formally included by TAP in the remainder of this overview.

Table 2. Systematic reviews for ALS

Light shading indicates related reviews: overlapping author lists or same review in different publication formats/updated

Citation	Publication years covered/ number of studies included	Content
Systematic reviews: organization of care		
Ng (Cochrane protocol; 2008)	Protocol; full review not yet available	Multidisciplinary care for ALS/MND
Systematic reviews: interventions		
Stone (2009)	1966-2006	Botulinum toxin or radiotherapy for sialorrhea
Benatar (Cochrane; 2009)	1966-2006	Treatment for familial ALS/MND
Bongioanni; Cochrane protocol, 2009)	Protocol; full review not yet available	Methods for informing people with ALS/MND of their diagnosis
Bongioanni (2008)	1966-2006: 2 RCTs	CNTF
Brettschneider (Cochrane; 2008)	1966-2007: no RCTs found	Drug therapy for pain
Dal Bello-Haas (Cochrane; 2008)	1966-2007: 2 RCTs	Therapeutic exercise for ALS/MND
Grundy (Cochrane protocol; 2008)	1950-present/review results not yet available	Treatment for sialorhea
Annane (Cochrane; 2007)	1966-2006: 8 RCTs	Nocturnal mechanical ventilation
Miller (Cochrane; 2007)	1966-2006: 4 RCTs	Riluzole for ALS/motor neuron disease.
Mitchell (Cochrane; 2007)	1966-2007: 3 RCTs	rhIGF-I for ALS/motor neuron disease
Orrell (Cochrane; 2007)	1966-2007: 9 studies	Antioxidant treatment
Radbruch (Cochrane protocol; 2007	Protocol; full review unavailable	Drugs for fatigue in palliative care
Sathasivam (Cochrane protocol; 2007)	1950- present Protocol; full review unavailable	Minocycline for ALS/MND
Ashworth (Cochrane; 2006)	1980-2006: 1 RCT	Treatment for spasticity in ALS
Leigh (Cochrane protocol; 2006)	Protocol; full review unavailable	Mechanical ventilation
Piepers (2006)	1985-2005: 12 studies	Non-invasive ventilation: survival, QoL, respiratory function, cognition
Bedlack (Cochrane protocol;2005)	Protocol; full review unavailable	Creatine for ALS/MND
Gruis (2005)	Cost-effectiveness model: utilities from literature	Early NIVPP
Tavakoli (2002)	Based on NICE (2001; below)	Cost-utility of riluzole by stage of disease
Stewart (2001)	1966-2000: 4 studies	Clinical effectiveness and cost-effectiveness of riluzole
Bryan (2001): update to Stewart with additional data from drug manufacturer		
NICE (2001): NHS guidance based on Stewart		
Langmore (2006)	1966-2005: no controlled trials available	Enteral tube feeding
Gruis (2005)	QoL and utilities from 2001 trial	Cost-effectiveness of early NIV
Chou (2004)	1966-2003: 98 reports of 101 RCTs	Skeletal muscle relaxants for spasticity
Garces (CCOHTA assessment; 2003)	"regularly updated": 4 RCTS and 2 systematic reviews	Riluzole: efficacy and safety
Leigh (Cochrane protocol; 2003)	1966- present): RCTs and quasi-randomized	Mechanical ventilation
Weber (Cochrane protocol; 2003)	1980-present	Treatment for cramps

Citation	Publication years covered/ number of studies included	Content
Jennings (2002)	1982-1999): 18 RCTS	Opiods for dyspnea
Total 158 included studies with some duplication likely		• **18 completed reviews for interventions; 3 related publications (NHS guidance development);** • **8 Cochrane protocols.**
Reviews with some characteristics of systematic methods but incomplete reporting, insufficiently focused research questions, and/or inadequate quality assessment of included studies: quasi-systematic		
Williams (2006)	1966-	Spirituality at the end of life
Andersen (2005)	-2005	10 central issues in diagnosis and clinical management identified for EB and consensus recommendations: • research questions not specified; • study selection unclear; • quality assessment not reported. • alignment of specific studies with recommendations unclear; • Print reference is summary report but full version not available on web.
Anderson (2005)	1985-2003: 4 controlled studies	Techniques to enhance peak cough flow and maintain vital capacity. • Quality assessment referenced but not applied to included studies; • Reported as narrative review.
Heffernan (2004)	Not reported	Nutritional management: • Global evidence ratings but study selection unclear; quality assessment not reported. • Alignment of specific studies with recommendations unclear; • reporting generally ambiguous.
Ginsberg (2002)	1966-2000	Cost-effectiveness of ALS treatments
Miller (1999)	1966-1997: 750 articles; study designs not reported or assessed beyond aggregated level of evidence.	AAN practice parameter: • Global evidence ratings but study selection unclear and quality assessment not reported. • Reporting generally ambiguous.
Van Schaik (1995)	1980-1994: 38 studies	Technical performance of ELISA: Anti-GM_1 antibodies to distinguish LMN and UMN diseases.
Total		**8 quasi-systematic reviews: interventions, diagnosis, ethics**

SUMMARY/DISCUSSION

ALS is a devastating disease of uncertain cause. It is related to other motor neuron disorders, with little consistency in staging, no treatment directed at a cure, and an inadequate evidence base. While investigators express hope for future developments, management options remain restricted to riluzole's modest benefit, followed by symptomatic and palliative care. This picture has not substantially changed in the last decade, with much basic research still directed toward clarifying pathogenesis and epidemiology.

Major concerns here, common to other areas of clinical research publication and to other TAP reviews, are poor quality of research, ambiguous reporting, and inadequate editing by journals. TAP

closely read over 150 full text articles to arrive at the meager inclusion tables of 18 systematic reviews and two subsequently published eligible studies.

ALS research efforts are further hampered by: low prevalence; possibly distinct forms of the disease that may or may not respond to interventions in the same way; highly variable clinical course; and the lack of a single unequivocal diagnostic marker or classification. Much of the research that is available in support of symptom control was conducted in patients with other diagnoses or directed to surrogate outcomes. Available economic analyses acknowledge reliance on incomplete data and models, stressing the continuing need for definitive studies.

Finally, while an animal model for one of the mutations underlying some cases of familial ALS is available, generalization of results in this setting to a broad ALS patient population would be problematic in event of effective interventions. The very limited evidence in support of some interventions should be viewed in context of the terminal diagnosis and few options for patients and their physicians.

No INAHTA member agencies reported organized systems of care specific to ALS within their healthcare systems, quite possibly reflecting the fact that organization of ALS care is not currently supported by research adequate for national policy.

Optimal structure and content for VHA ALS services may be uncertain, but scope for VA clinical and health services research is not. Andersen (2005) and the EFNS Task Force detail a research agenda that remains valid:

1. *"Further studies of more specific diagnostic tools are needed, in particular in relation to cervical spondylotic myelopathy, inclusion body myositis and motor neuropathies.*
2. *There is no data on the effects of MD clinics on quality of life or care burden – the generation of such data would be beneficial.*
3. *Further studies are required to confirm the benefits of MD clinics, and to identify the factors that effect outcome.*
4. *Further studies are required to optimize the symptomatic treatment of ALS patients, in particular therapies for treating muscle cramps, drooling and bronchial secretions.*
5. *Better criteria for defining the use of PEG ad PRG, and NIV and TV are urgently needed.*
6. *Further studies to evaluate the effects of PEG/PRG, cough-assisting devices and ventilation support on quality of life and survival are advocated.*
7. *Further studies are required to evaluate the language dysfunction and its treatment in ALS.*
8. *Studies of the medico-economic impact of more expensive procedures (NIV, TV, cough-assisting devices, advanced communication equipment) are needed."*

All systematic reviews for riluzole (Appendix Table 4), the only drug to have demonstrated modest benefit in ALS, include the same four trials, which in aggregate provide only incomplete efficacy information up to eighteen months (Bryan; 2001; Table 2). Stewart (2001) suggests guidance for future riluzole research:

> *"Ideally, reliable evidence from further trials is necessary to answer the many uncertainties that exist. These should include a substantial incident population, with long-term (5-year) survival, follow-up, and collection of health economic and quality-of-life data. Further analysis of existing trial data and information from ALS databases may provide additional useful data in the short term."*

Gordon (2009) provides context for novel study design designations in ALS research:

> *"Resources restrict the number of agents that can be studied in ALS. Reduced funding, the high cost of conducting a trial, and the rarity of the disease limit how many clinical trials can be performed. The focus is increasingly centered on efficient early phase trial designs that screen candidate therapies, identifying those that are most promising—whether symptomatic or*

> *neuroprotective—for the few Phase III trials that can be conducted each decade. Adding to the efficiency of some of these new designs is the absence of a placebo arm. Several early phase trial designs can be conducted without a placebo group and are being newly utilized in ALS and other neurologic conditions. Dose-ranging, futility, and selection trials are examples…"*

Uncontrolled studies are not new to clinical research: case series have a high risk of selection bias and are used to generate (but not to test) hypotheses. Such series are not currently accepted as demonstrations of efficacy by the FDA and are unlikely to be in the future (Simmons, 2009).

Turner (2009) reiterates with particular clarity the overall status of ALS:

> *"Amyotrophic lateral sclerosis (ALS; motor neuron disease) is a relentlessly progressive disorder. After half a century of trials, only one drug with modest disease-modifying potency – riluzole—has been developed. The diagnosis of this disorder is still clinical and there is a pronounced delay between the onset of symptoms and diagnosis, possibly beyond the therapeutic window. Beside quantification of involvement of the cortico-spinal tract and extramotor areas is inadequate and functional rating scales, forced vital capacity, and patient survival have been the measures of therapeutic response so far. Potential biomarkers that are sensitive to the progression of disease, which might enhance the diagnostic algorithm and provide new drug targets, are now being identified from analysis of the blood and cerebrospinal fluid, as well as from neuroimaging and neurophysiology studies. In combination, these biomarkers might be sensitive to early therapeutic effects and would reduce our reliance on animal models, which have uncertain relevance to sporadic ALS in human beings. Such biomarkers might also resolve complexities of phenotypic heterogeneity in clinical trials…."* Turner (2009).

IN-PROGRESS RESEARCH

The Cochrane protocols (reviews in planning stage) listed in Table 2 and Appendix Table 4 indicate clinical issues likely to be clarified by reviews in the foreseeable future, while Table 3 lists ongoing ALS studies likely, once completed and published, to be eligible for this document's reviews.

Table 3. In-progress studies

Retrieved from www.clinicaltrials.gov on June 3, 2009.
Listed: RCTs likely to be eligible for this overview's systematic reviews.
Not listed: inactive, suspended, withdrawn, or completed trials; pilot/feasibility/Phase I trials.

Name/Purpose	Sponsor/location	Design/outcomes	Estimated completion
Talampanel for ALS	Teva Pharmaceutical Industries	RCT: efficacy and safety	2010
SB-509 for ALS	Sangamo Biosciences	Phase II: • Repeat dosing effect on disease progression (ALSRFS); • Safety at 11 months.	2010
Arimoclomol for ALS (SOD1+ fALS)	FDA Orphan products development; Mass General Hospital; Emory University	Phase II/III: • 100mg bid; • Safety and tolerance; • Reduction in rate of progression by ≥ 30%.	2012
Olanzapine for cachexia in ALS	Charite University, Berlin Germany	Phase II/III: Olanzapine plus Riluzole • Effectiveness and tolerability; • Undesired weight loss ≥20% less than placebo; • 51 weeks of treatment	2011
Ceftriaxone for ALS	Mass General, Boston; NINDS	Phase II/III: • Safety and efficacy; • Survival at duration of study (1yr of treatment); • ALSFRS;	2012
E0302 (mecobalamin) for ALS	Eisai Medical Research inc.	Phase II/III: • Safety and efficacy; • Survival; • ALSFRS	2013
MVCI-186	Mitsubishi Tanabe Pharma Corp	RCT: • Safety and efficacy of long-term intermittent treatment; • ALSFRS at 3 months; • Time to death or a certain state (inability to walk alone, failure of arm function, tracheostomy, respirator, tube feeding); • Adverse events	2009
Olesoxime added to Riluzole	Trophos European Commission	Phase II/II: • 18-month survival; • Survival without tracheostomy, chronic IV or NIV; • ALSFRS	2011

GCSF, granulocyte colony stimulating factor
NINDS, National Institute of Neurological Disorders and Stroke

APPENDIX

Table 4. Systematic reviews for ALS

Quasi-systematic reviews listed in Figure 1 not included;
Review entries (citations in bold and shaded cells) followed by subsequently-published eligible studies (citations in clear cells or policy statements based on reviews

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
Benatar (2009)	**Cochrane review** **Is there a difference in the response to treatment between patients with sporadic and familial forms of ALS?** • Multiple databases, 1966-2006; • RCTs including patients with both familial and sporadic ALS; • RCT investigators contacted to supply data (familial or sporadic, treatment assignment, survival, ALSFRS) if not published	**Studies:** • Reviewers could not obtain data for 25 potentially eligible studies: 17 trial authors could not be contacted, and 8 were unwilling to supply data; • 4 studies included in review: 3 NEALS trials (creatinine, celecoxib or topiramate Vs placebo); conducted in US; I trial (creatinine monohydrate Vs placebo) in Netherlands. **Outcomes:** No statistical evidence for different responses to treatment in patients with familial versus sporadic ALS. **Conclusions:** *"Future RCTs should document whether patients with familial ALS/MND are included and the presence or absence of a mutation in the superoxide dismutase-1 gene amongst those with familial ALS/MND."*
Bongioanni (2009)	**Cochrane protocol** **Effects and effectiveness of different methods for informing people of ALS/MND diagnosis:** • Randomized or quasi-randomized studies in adults ≥17 with el Escorial possible, probable, or definite diagnosis; • Any intervention designed to break the bad news about ALS/MND; interactive (face to face) distinguished from passive (provision of written material; • Outcomes: patient coping and adjustment by scale or questionnaire, immediately and at 6 months; patient perceptions of coping, family relationships, anxiety /depression; QoL; knowledge of ALS; carer's perceptions, knowledge, understanding; patient and carer satisfaction.	Protocol; full review not yet available.
Stone (2009)	**Evidence for effectiveness and toxicity of botulinum toxin or radiotherapy for sialorrhea:** • Multiple databases, 1966-2006; • Studies in humans published in English; • Reference lists and clinical specialists for unpublished, hand searching individual journals; • Botulinum toxin and radiotherapy separately analyzed;	**5 botulinum toxin studies:** • 2000-2006, enrolling a total of 28 patients; • 2/5 studies: El Escorial definite diagnosis, not reported in remainder of studies; • 3/5 studies: patients had failed to achieve adequate control with anticholinergic medications; remaining 2 reported only "disabling or uncontrolled"; • Studies varied: injection techniques; dose/repetition; • 2/5 studies used reliable and valid outcome measure (technetium scintigraphy); others used number of paper tissues consumed daily or no quantitative assessment of outcome;

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
		• 4 studies using intra-glandular injection: no adverse effects; 2/4 found positive effects on salivary secretion, and QoL; • 2 patients in studies using retrograde injection did have significant adverse effects but positive effects on secretion rate. **Radiotherapy:** • 2 studies with 27 patients; • Both showed positive effect on salivary secretion rate. **Overall:** • Small numbers of studies, small sample sizes, and poor reporting make conclusions impossible. • *"There is some evidence that both botulinum toxin and radiotherapy are well tolerated effective treatments for persistent sialorrhea in patients with ALS and that the duration of action is up to three months with botulinum and six months with radiotherapy."*
Jackson (2009)	**Double-blind RCT: Injected botulinum toxin for sialorrhea:** • 20 patients (probable or definite) recruited from ALS centers at universities of Kansas, Carolinas, and Texas; • Baseline assessment on day of injection (2 each bilateral parotid and submandibular glands) under EMG guidance; • FU weeks 2, 34, 8, and 12; • After 12 week blinded study, patients had option to enroll in open-label 3 month extension with dose adjustment by unblinded investigator; • Outcomes: global self-assessment of change 8 weeks – post-injection (primary); caregiver assessment; suction frequency (secondary).	**Groups well-matched at baseline** • Except for gender: 36% male (botox) Vs 67% (placebo); • Proportion of patients reporting significant improvement: botox, 90%; placebo, 11%; at 4 weeks; marked improvement (botox 60%; placebo 11%); • Differences declined after 4 weeks; • Trends in secondary outcomes NS; • No significant adverse effects or changes in FVC. **High quality study:** • Treatment allocation, power calculation and blinding reported; • Power calculation may have been post hoc. **Conclusions:** *"Although a beneficial effect of botulinum toxin for the treatment of medically refractory sialorrhea appears to be well-established by these data, further studies are clearly needed to clarify optimal dosing both in terms of total dose as well as the distribution between the parotid and submandibular glands. Either increasing the total dose and/or individualizing the distribution of the dose for each patient outside the restrictions of a randomized study might allow for a more prolonged duration of action. In addition, it remains unclear whether there may be potential differences between botulinum toxin types A and B in terms of safety, efficacy, or duration of action."*
Bongioanni (2008)	**Cochrane review:** • Efficacy of CNTF in ALS; • Multiple databases, -2006; • Placebo-controlled RCTs; • Subjects with El Escorial probable or definite diagnosis treated with CNTF for a least 6 months; • Primary outcome: survival;	**2 trials:** • Total enrollment, 1300 ALS patients; • Subcutaneous recombinant CNTF Vs. placebo; • Methodological quality adequate; • NS difference between groups for survival: RR, 1.07 (CI, 0.81-1.41); • NS differences for secondary outcomes except for rate of adverse events at higher doses of CNTF.

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	• Secondary outcomes: muscle strength, respiratory function, changes in QoL; adverse effects (cough, asthenia, nausea, anorexia, weight loss, increased salivation).	**Conclusions:** *"Ciliary neurotrophic factor has no effect on amyotrophic lateral sclerosis progression. At high concentrations, several side effects were observed. A combination of ciliary neurotrophic factor with other neurotrophic factors (as suggested by results on animal studies) and more efficient delivery methods should be tested."*
Brettschneider (2008)	**Cochrane review** • Evidence for efficacy of drug therapy in relieving pain in ALS; • Adverse effects; • Influence on survival and QoL. • Multiple databases, 1066-2007; • Randomized or quasi-randomized trials.	**No RCTs identified; no analyses conducted.** **Conclusions:** *"There is no evidence from randomized controlled trials about the management of pain in ALS. Further research on this important aspect of palliative care in ALS is needed. Randomized controlled trials should be initiated to determine the effectiveness of different analgesics for treatment of pain in ALS."*
Dal Bello-Haas (2008)	**Cochrane review:** **Randomized and quasi-randomized studies of exercise in individuals with ALS or MND:** • Patients with El Escorial definite, probable, probable with laboratory, or possible ALS; • Interventions/controls: progressive resistance, strengthening, endurance or aerobic exercise/ Vs. no exercise or standard rehabilitation; • Multiple databases. 1966-2007; no language restriction • Primary outcome: improvement in functional ability, decline in disability, or reduction in rate of decline measure by validated instrument at 3 months; • Secondary outcome (3 months): improvement in psychological status, QoL, reduction in rate of decline for muscle strength or endurance, or adverse event rate.	**2 RCTs:** • 52 patients total; • Twice daily moderate load exercise Vs "usual activities" (25 patients); 3x weekly moderate intensity resistance Vs stretching (27); • 2 trials combined at 3 months: significant weighted mean improvement in ALSFRS in favor of exercise but NS differences in QoL, fatigue, or muscle strength. **Conclusions:** *"The only studies detected were too small to determine to what extent muscle strengthening exercises for people with ALS are beneficial, or whether exercise is harmful. There is a complete lack of randomized or quasi-randomized clinical trials examining aerobic exercise in this population. More research is needed."*
Grundy (2008); Cochrane protocol	**Trials of interventions designed to minimize sialorrhea:** • Randomized and quasi-randomized including non-blinded; • Patients >18 diagnosed with El Escorial probable or definite MND/ALS; • Interventions compared with each other, placebo, or no treatment: any drug administered by any route; botulinim toxin injected to parotid and/or submandibular glands; radiotherapy to salivary glands; surgical techniques (ligation or parotid or submandibular ducts); other treatments (complementary therapies; • Primary outcomes: subjective improvement in the short (1-12 weeks) or longer (> 12 weeks) term; • secondary outcomes: short or longer term reduction in	**Protocol:** review results not yet available.

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	saliva production by an objective measure (weight of swabs or tissues used); adverse effects.	
Ng (2008); Cochrane protocol	Does organized multidisciplinary care achieve better outcomes than the absence of such services in people with ALS/MNZD? • What types of programs are effective and in which settings? • Does greater intensity (time and/or expertise) of rehabilitation lead to greater gains? • Which specific outcomes are influenced (survival, dependency, social integration, mood, quality of life)? • Are there demonstrable cost-benefits for multidisciplinary care in MND? Studies to be included: RCTs or clinical controlled trials	Protocol only: full review not available.
Annane (2007)	**Cochrane review:** **What is the efficacy of nocturnal mechanical ventilation in relieving hypoventilation-related symptoms and in prolonging survival in people with neuromuscular or chest wall disorders?** • Multiple databases, 1966-2006; • Eligible diagnoses: Arnold-Chiari malformation; CNS trauma; cerebro-vascular disorders; congenital or acquired disorders of breathing; myelomeningocele; SCI; ALS; spinal muscle atrophy; polio and post-polio syndrome; congenital childhood hypotonia; Guillian- Barré syndrome; infantile botulism; muscular dystrophy; myotonic dystrophy; phrenic nerve paralysis; myasthenia gravis; kyphoscoliosis; thoracic wall deformations; thoracoplasty; • RCTs: participants with neuromuscular or chest wall disorder-related stable chronic hypoventilation of all ages and any degree of severity; • Receiving any type and mode of nocturnal mechanical ventilation for at least 3 hrs/night; • Reporting: short- or long-term reversal of hypoventilation related clinical symptoms; unplanned hospital admission; short- or long-term reversal of hypercapnia; or improvement of lung function or sleep breathing disorders.	**8 RCTS:** • 144 subjects; • RR of "no improvement of hypoventilation-related clinical symptoms" reported in only one trial (N = 10): NS, 0.09 (CI, 0.01-1.31); • RR of "no reversal of daytime hypercapnia", short- term following nocturnal ventilation: significant in favor of treatment; RR, 0.37 (CI, 0.20-0.65); • WMD, nocturnal mean oxygen saturation: 5.45% (CI, 1.47-9.44), or more improvement with ventilation; • Most outcome measures found no significant long-term differences, ventilation Vs no ventilation; • Based on 3 studies, estimated risk of death was reduced with ventilation (0.62; CI, 0.42-0.91); • Considerable and significant heterogeneity among trials, possibly due to differences in study populations; • Most trials did not assess secondary outcomes; • 2 crossover trials suggested no difference in daytime hypercapnia or sleep parameters; • No data could be summarized for invasive Vs non-invasive comparisons or intermittent positive pressure Vs negative pressure., **Conclusions:** *"Current evidence about therapeutic ventilation is weak, but consistent, suggesting alleviation of the symptoms of chronic hypoventilation in the short- term. In three small studies survival was prolonged mainly in participants with motor neuron diseases. With the exception of motor neuron disease, further larger randomized trials are needed to confirm long-term beneficial effects of nocturnal mechanical ventilation on quality of life, morbidity and mortality, to assess its cost-benefit ratio in neuromuscular and chest wall diseases and to compare the different types and modes of ventilation."*
Mitchell (2007)	**Cochrane review** **What is the efficacy or recombinant human insulin-like growth factor I in amyotrophic lateral sclerosis?**	**Three RCTs,** one excluded for use of other outcome scale. **2 RCTs**: • 449 subjects total;

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	• Multiple databases, 1966-2007; • RCTs involving rhIGF-I in adults with El Escorial probable or definite ALS; • Primary outcome: Change in AALSRS at 9 months; secondary, changes at monthly intervals up to 9 months; change in QoL, survival, adverse events.	• Combined analysis: WMD at 9 months, -4.75 (CI, -8.41—1.09), significant in favor of treatment; • Secondary outcomes: NS trends favoring treatment. **Conclusions:** *"The available placebo controlled trials do not permit a definitive assessment of the clinical efficacy of rhIGF-I on ALS. More research is needed and one trial is in progress. Future trials should include survival as an outcome measure."*
Miller (2007)	**Cochrane review** • Efficacy of riluzole in prolonging survival; • And in delaying survival surrogates (tracheostomy, mechanical ventilation). • Multiple databases, 1966-2006; • RCTs comparing riluzole to placebo; • Outcomes: tracheostomy-free survival at all time points with riluzole 100 mg; neurologic function; muscle strength; adverse events.	**4 RCTs with 1477 patients total (3 contributed to meta-analysis; one lacked sufficient detail)** • 974 riluzole; 503 placebo; • Methodologic quality acceptable; trials easily comparable (one included older patients with more advanced disease; another used multiple primary endpoints); • Therapeutic effects of riluzole at 100 mg in homogenous patients from 2 trials; significant (P= 0.039): significant heterogeneity (P<0.0001) when 3rd trial (more seriously affected older patients) was added and effects fell just short of significance and increase in median survival for riluzole group was modest (2-3 months); • Modest impact on functional measures. **Conclusions:** *"Riluzole 100 mg daily is reasonably safe and probably prolongs survival by about two to three months in patients with amyotrophic lateral sclerosis."*
Orrell (2007)	**Cochrane review** **Effects of antioxidant treatment** • RCTs or quasi-randomized studies; of any agents considered to have antioxidant effects: vitamins C or E; seleginine; N-acetyl cysteine; dehydroepiandrosterone; N-acetyl methionine; dithiothreitol • Multiple databases, 1966-2007; two studies in Polish translated.	**9 trials:** • 830 patients; • 7 of the trials were non-crossover: 383 treatment patients; 367 placebo controls. **Individual studies:** no significant effects for vitamin E (500 mg twice daily or1g 5 times daily); acetylcysteine (50 mg/kg daily subcutaneous injection); combination of L-methionine 2g/ vitamin E 400 international units/selenium 0.04mg 3 times daily; **Meta-analysis of 4 studies:** no significant effect for any antioxidant tested in primary or secondary outcomes. **Conclusions:** *"There is insufficient evidence of efficacy of individual antioxidants, or antioxidants in general, in the treatment of people with amyotrophic lateral sclerosis One study reported a mild positive effect, but this was not supported by the analysis we used. Generally the studies were poorly designed, and underpowered, with low numbers of participants and of short duration. Further well-designed trials of medications such as vitamin C and E are unlikely to be performed. If future trials of antioxidant medications are performed, careful attention should be given to sample size, outcome measures, and duration of the trial. The high tolerance, safety, and relatively low cost of vitamin C and E, and other considerations related to the lack of other effective treatments for amyotrophic lateral sclerosis, explain the continuing use of these vitamins by physicians and people with amyotrophic lateral sclerosis. While there is no substantial clinical trial evidence to support their clinical use, there is no clear contraindication."*

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
Radbruch (2007)	**Cochrane protocol** **To determine the efficacy of pharmacological treatments on non-specific fatigue in palliative care.** • Patients in an advanced stage of their diseases: cancer (concurrent anti-cancer treatment during study eligible); lung failure; cardiac failure; HIV/AIDS; • RCTs in humans comparing drugs for fatigue Vs alternatives and/or no treatment; • Interventions: psychostimulants; amantidine; corticosteroids; donepsil; antidepressants; others; but not erythropoietic agents, transfusion, or drugs targeting cytokines; • Outcomes; self-reported fatigue, or estimates by careers/medical staff; measure by validated instruments; improvement of fatigue by 33%; • Other outcomes; asthenia; weakness; tiredness; sedation; exhaustion; burden of treatment (adverse events; morbidity/mortality).	Protocol; full review not yet available.
Sathasivam (2007)	**Cochrane protocol** **Evidence from RCTs on benefits or harms of minocycline for ALS/MND:** • 1950-present; • Randomized trials comparing minocycline to placebo, no treatment or another treatment in patients with El Escorial clinical diagnosis; • If minocycline given in combination, comparison group must have received same other treatment; • Primary outcome: rate of change in ALSFRS at ≥6 months; secondary, rate of change in function by any other validated scale; change in muscle strength; change in FVC; QoL; adverse events; tracheostomy-free survival.	Protocol; full review unavailable.
Ashworth (2006)	**Cochrane review** **To systematically assess treatments for spasticity in ALS/MND** • Multiple databases plus queries to investigators, 1980-2006; • RCTs or quasi randomized trials: subjects with El Escorial probable or definite ALS; • Eligible interventions: physical therapy modalities; prescription or non-prescription drugs; chemical neurolysis; surgery; alternative therapies; • Primary outcome: reduction in spasticity at ≥3 months on	**One RCT:** • 25 patients; • Moderate intensity endurance type exercise (15 minutes twice a day) Vs "usual activities"; • At 3 months: exercise group had significantly less spasticity overall. Mean reduction, -0.43 (CI, -2.03-0.17) Vs increase in controls,+0.25 (CI, -0.46 - +.96); • Mean change between groups for Ashworth scale NS: -0.68 (CI, -1.62- +0.26). **Conclusions:** *"The single trial performed was too small to determiner whether individualized moderate endurance type exercises for trunk and limbs are beneficial or harmful. No other medical, surgical, or alternative treatment has been evaluated in a randomized fashion in this patient population. More research is needed."*

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	Ashworth or modified Ashworth spasticity scale; • Secondary outcomes: validated measures based on history, physical exam, physiology, or function: QoL; serious adverse events; or cost.	
Langmore (2006)	**Cochrane review** **To examine the efficacy of PEG or other tub feeding placement in ALS: survival; nutritional status; QoL; major complications:** • Multiple databases, 1966-2005; • RCTs and quasi-randomized studies non-randomized controlled studies (background and discussion only) in absence of RCTs.	**No RCTs; 155 articles representing controlled studies worthy of consideration, of which 10 were controlled (cohort or case-control):** **Survival outcomes:** • Analyzed in 3 studies; • Univariate analyses showed no difference in overall survival, PEG Vs. oral feeding (925 days Vs. 760; p = 0.09); • Multivariate analyses found better survival with PEG (P = 0.02) in bulbar but not spinal onset patients. **Conclusions: "***There are no randomized controlled trials to indicate whether enteral tube feeding is beneficial compared to oral feeding for survival. The 'best' evidence to date, based on retrospective controlled studies, suggests an advantage for survival in all people with amyotrophic lateral sclerosis/motor neuron disease, but these conclusions are tentative. Evidence for improved nutrition is also incomplete but tentatively favorable. Quality of life has only been addressed by a few researchers and needs more serious attention."*
Piepers (2006)	**What are the effects of NIV on survival, QoL and other outcomes?** • Multiple databases, 1985-2005; • Observational studies or RCTs using ALS patients receiving NIV and reporting QoL, survival, respiratory function/symptoms, or cognition; • Quality criteria: internal validity; retro-Vs prospective; duration of FU; completeness of data reporting; adjustment for confounders; validated outcome measures.	**12 studies met inclusion criteria:** • Observational: 4 retrospective; 7 prospective; • 1 RCT; • Settings: neurology departments; specialized ALS or neuromuscular centers, respiratory departments; two studies did not specify site; • Number of subjects, 12-122; median duration of FU, 1.5-100 months; mean patient age, 59.3 yrs (55-62.2); • Two observational studies used control groups: ALS patients with normal respiratory function matched for age, sex, disease severity; and patients who did not tolerate NIV; • RCT control group: first 10 patients recruited who were not treated with oxygen bronchodilators or other palliative measures; next 10 received NIV (evidence class II); **VOTE COUNT:** **Survival** • 7 studies reported survival: in all cases prolonged; • 4 studies found longer survival for patients tolerating NIV Vs those who did not; • Cumulative survival longer in patients without bulbar symptoms AND with NIV Vs no NIV' • One study found longer survival with NIV Vs palliative care. **QoL**

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
		5 studies reporting QoL used 5 different instruments or sub-scales: all found positive effects; **Respiratory function** • 6 studies examined impact of NIV: 2, no change in rate of decline in patients who tolerated; 1 NS improvement in pCO_2; 1, improvements in pCO_2 and pO_2 but worse FVC%. **Respiratory symptoms** • 3 studies reported: 1, significant improvement in sleep apnea; 1, 3/6 patients on NIV improved, 1, reduction in dyspnea, headache, and concentration difficulties. **Cognition** 1 study reported significant improvement after initiation of NIV. **Conclusions:** *"Studies on the use of NIV in ALS differ in study design and endpoint definitions. All studies suggest a beneficial effect on QoL and other outcome measures (Class II-III evidence). Well-designed randomized controlled trials comparing the effect on QoL and survival have not been performed."*
Carratù (2009)	**Case series (retrospective) with control:** • ALS patients at 3 academic medical centers in Italy (Catania, Bari, Naples) with FVC <75% and nocturnal respiratory insufficiency who received NIPPV; • Controls: ALS patients with FVC> 75% or < 75% and refused or were intolerant of ventilation.	**72 consecutive patients evaluated for pulmonary function:** • 44 had FVC > 75% (controls); 16 < 75% received NIPPV; 12 refused or intolerant; • Increased survival at 1 yr in < 75% treated Vs refused or intolerant (p = 0.02); • Median rate of FVC rate of decline slower in NIPPV Vs untreated (CI, 0.72-1.85; p<0.001). **Conclusions:** *"This report demonstrates that early treatment with NIPPV prolongs survival and reduces decline of FVC % in ALS."*
Bedlack (2005)	**<u>Cochrane protocol</u>** **Effects of creatine for treating ALS:** • Controlled trials: randomized and quasi-randomized in subjects with ALS (any state of clinical pattern) and reporting trachestomy-free survival; • Secondary outcomes: overall survival; survival at 6 months and 1 year; physical function on ALSFRS (1, 6, 12 months); adverse events; QoL. • Synthesis and quality assessment according to Cochrane Handbook.	Protocol; full review not yet available.
Gruis (2005)	**Cost-utility analysis:** **What is the benefit in health state utility that early NIV in ALS patients must achieve to be cost-effective?** • Outcome: % utility gained through NIPPV in relation to common willingness-to-pay thresholds ($50,000 or	**Average patient receiving early NIPPV:** • 0.59 QALY; • Cost of $1773. **Average patient not receiving early NIPPV:**

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	\$100,000/QALY); • Decision tree model: NIPPV starting at time of diagnosis Vs no NIPPV for hypothetical cohort of patients with recent diagnosis of ALS; • Markov model shifted patients through disease states (mild, moderate, terminal, death) at probabilities of progression over time from Tavakoli (2002; below) and beginning in mild state; • Assumed that both groups would receive NIPPV when FVC fell to < 50%; • Reference case: 20% benefit in health state utility in early NIPPV group Vs no NIPPV group; • Sensitivity analyses for all variables across ranges; • Costs based on Medicare 2004 fee schedule in US\$.	• 0.54 QALY; • Cost, 0. **Cost-effectiveness :** • Incremental ratio, \$33,801; • NIPPV has incremental cost-effectiveness ratio of \$50,000 as long as utility for patients receiving NIPPV is at least 13.5% higher at each stage than those without NIPPV; i.e., early NIPPV is cist-effective as long as NIPPV beginning at diagnosis improves HRQL by at least 13.5%; • For a willingness-to-pay threshold of \$100,000/QALY, increase in HRQL with NIPPV would need to be 6.8% or greater to be cost-effective. **Conclusions:** *"If early use of NIPPV is shown to improve HRQL in future studies, it is likely to be a cost-effective treatment. Further trials of early NIPPV initiation in ALS patients are warranted, and supported from a cist0-effectiveness perspective."*
Chou (2004)	**Systematic review commissioned by OHRC:** • What is the comparative efficacy and safety of different muscle relaxants? • Are there subpopulations of patients for which one muscle relaxant is more effective or associated with fewer adverse effects? • Multiple databases, 1966-2003; • Selection criteria: English-language; adult or pediatric patients with spasticity (UMN syndrome) or a musculoskeletal condition (peripheral condition resulting in muscle or soft tissue pain or spasm); • Excluded: studies conducted with obstetric, dialysis, restless leg syndrome, nocturnal myoclonus, HIV, or cancer patients; • Interventions: baclofen, carisoprolol, chlorzoxazone, uclobenzaprine, ordantrolene, tizanidine; others (benzodiazipines, quinine, tricyclic antidepressants, gabapentin, clonidine) when directly compared to included skeletal muscle relaxant; but not eligible were trials combining muscle relaxant with analgesic unless comparison arm used the same combination. • Outcomes: relief of spasm or pain, functional status, QoL, adverse effects (sedation, weakness, addiction, abuse), but not non-clinical outcomes (EMG or spring tension measurements).	**After exclusions, 98 reports with data from 101 RCTs** enrolling patients with spasticity or musculoskeletal conditions and 4 systematic reviews: • External validity of trials difficult to assess due to incomplete reporting; • Only one review was of high quality. • No pattern suggested that one muscle relaxant was any better than others; • Meta-analysis not possible due to heterogeneity of study designs, interventions, outcomes. • No information on comparative efficacy in subpopulations defined by age, sex, race, or gender. **Conclusions:** *"The lack of high-quality evidence regarding this class of medications is concerning given their wide use. Without better evidence regarding differential safety or efficacy, payers may be forced to rely disproportionately upon cost as a differentiating factor in choosing among medications in this class."*
Garces (2003)	**Potential benefits and harms of riluzole when used for**	**4 RCTS had been included in previous reviews:**

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	patients with ALS: • All-cause mortality, morbidity, QoL during treatment; • Multiple databases, "regularly updated"; and grey literature • RCTs and systematic reviews.	• 1 compared several riluzole doses to placebo; 3 compared100 mg to placebo; • 3 enrolled similar patients (18-75 yrs and diagnosed< 5 yrs); the fourth enrolled patients > 75 or> 5 yrs from diagnosis; • Meta-analysis: riluzole provided additional 2-3 month tracheostomy-free survival; pooled estimate showed significant heterogeneity; • All-cause mortality across 2 trials: effect of riluzole similar in direction and magnitude to tracheostomy-free survival; • Number of tracheostomies was small: no detectable difference between tracheostromy-free and all cause mortality; • Trials reported only partially: serious adverse events, patient withdrawals due to adverse events; • Patients > 75 or with long term illness reported fewer serious adverse events, suggesting that riluzole could reduce serious morbidity, but more adequate reporting is needed. **Conclusions:** *"Riluzole has the potential to reduce serious morbidity in certain patients at the cost of causing some drug intolerance (withdrawals due to adverse events). There is no information available to describe its impact on quality of life or time to tracheostomy alone."*
Weber (2006)	**Cochrane protocol: Treatment for cramps in ALS/MND** • RCTs and quasi-RCTs in patients with E; Escorial probable or definite diagnosis; • Interventions: or medications or physical treatments reported to potentially relieve cramps; • Outcomes: absolute change in analog cramp rating scale after 1 month of treatment (primary); duration of cramps or cramp-days (secondary); • Critical appraisal/statistical analysis by Cochrane Handbook.	**Protocol: results not yet available**
Leigh (2003)	**Cochrane protocol:** **efficacy of mechanical ventilation in ALS/MN** • RCTs and quasi-; • 1966-present; • Clinical diagnosis of ALS/MND: pure mixed UMN/LMN with supportive electromyelogram; any pattern; any state of disease; but particularly those without significant bulbar symptoms; • Interventions: all forms of NIV (nasal or facial mask or mouthpiece) and tracheostomy assisted ventilation; • Outcomes: survival (primary); 1 month or 6 month survival, QoL, adverse events (secondary); • Cochrane methods for quality assessment and statistics.	**Protocol: results not yet available**
Jennings (2002)	**What is the effectiveness of opiods in the management of dsypnea?**	**18 RCTs with cross-over design:** • 96 patients total; largest sub-group had COPD;

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	• RCTs involving any dose of any opiod administered to alleviate breathlessness in patients with dyspnea caused by any disease; • Jadad scale used to rate quality of studies; • Primary outcome: subjective assessment of breathlessness recorded at end of exercise; • Secondary outcomes: exercise tolerance (duration, distance, or maximum power); QoL; arterial blood gases; oxygen saturation; treatment-related adverse effects; • Excluded: studies reporting breathlessness at fixed point during exercise.	• 9 trials used oral or parenteral opiods, 9 nebulized; • 5 studies not included in meta-analysis because data not reported to make inclusion possible; • Meta-analysis: highly significant positive effect of opiods on breathlessness with significant heterogeneity among studies; • Side effects reported for oral opiods: drowsiness, nausea, vomiting, dizziness, opiod withdrawal syndrome; patient withdrawal from study, constipation; • Nebulized opiod adverse effects reported: bitter taste, mouth, prickling sensation in throat. **Conclusions:** *"This review supports the continued use of oral and parenteral opiods to treat dyspnea in patients with advanced disease. There are insufficient data from the meta-analysis to conclude whether nebulized opiods are effective, but the results from included studies that did not contribute to the meta-analysis suggest that they are no better than nebulized normal saline."*
Tavakoli (2002)	**Long-term economic evaluation in UK:** • Review of QoL and discounting utilities from NICE (2001; below); • Riluzole for ALS Vs best supportive care; • Update on determination of disease phase prolonged by Rilluzole; • QoL of extension offered by riluzole. Cost-utility of Riluzole and cost-effectiveness of therapy: • Markov model using cohort of 954 patients from RCT, 1992-94; • Costs: acquisition of Riluzole; bimonthly monitoring; • Patient-assessed utilities by disease state: mild (state1), moderate (2), severe (3), and terminal (4).	• Base cost per year of life gained (Standard Gamble utility scores): £15,192; • Cost/QALY: £22,236; SD, £612; • Riluzole on average increases survival in ALS by 5 months, with 4 months in disease state 2 where QoL is relatively high; but model is sensitive to method of estimating transition through disease states; **Conclusions:** *"The results of the Markov model suggests an increased life expectancy of over 6 months, of which 1 month is spent in health state 1and 4 months is spent in state 2, where functional status is still relatively good. However, this gain in life expectancy, although modest, should be put in context considering that median survival is just 2.5-5 years from diagnosis. Furthermore, the direct cost to careers and their families as well as direct cost to the community services can be significant. These costs could not be included in the present study due to the perspective of the analysis, but the incremental QALYS gained could be interpreted as potential savings in these areas."*
Stewart (2001)	**Clinical and cost-effectiveness of riluzole:** • RCTs and economic studies: database searches and manufacturer; • Included: studies investigating effectiveness, cost-effectiveness, safety, QoL/patient satisfaction in MND without restrictions on age or sex.	**Four studies:** • 3 compared 100 mg riluzole daily to placebo; one used doses of 50, 100, 200 mg daily; • 3 had broadly similar patient eligibility criteria; one recruited patients ineligible for other trials (older or more ill; FVC< 60-%); • All 4 trials reported tracheostomy-free survival ; • Combined results favored riluzole: HR for trsacheostomy-free survival, 0.88 (CI, 0.75-1.02); • No evidence that effectiveness differed by site of onset; • No evidence of significant differences in daily doses of between 50 and 200mg; • There was evidence of statistical heterogeneity (p = 0.09) without clear explanation beyond chance; • Riluzole dies not improve symptoms: combined data on functional status indicated small reduction in rate of functional deterioration but clinical significance was not clear; • Large proportion of patients in riluzole and control groups reported adverse events for little overall difference between groups;

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
		• No evidence available for outcomes beyond 18 months. **Conclusions:** *"There is limited evidence of a modest benefit in tracheostomy-free survival for patients taking riluzole. However, the evidence is restricted and uncertainty remains as to the true benefit of riluzole; the CI is wide and compatible with little or no difference between riluzole and placebo. When costs and the health economic impact are considered when extrapolating survival beyond that observed in trials, the uncertainty about whether the benefits are wroth the costs is magnified. Even under the most optimistic assumptions, riluzole at best only postpones death for a few months, and does not preclude the need for supportive care and practical help."* *If riluzole were to be made available to all patients in whom it is not contraindicated, the annual cost to the NHS would be about £8.4 million, assuming all these patients would wish to take it. Many patients, given accurate information, may choose not to. Patients should be made aware that riluzole does not cure ALS; accurate patient information is essential."*
NICE (2001)	**Guidance on the use of riluzole (Rilutek) for the treatment of motor neuron disease**	**Four trials:** • Riluzole was associated with a relative reduction in hazard ration for tracheostomy-free survival (0.88; CI, 0.75-1.02), with evidence of heterogeneity across the 4 trials; • Pooled data on functional status indicated a small reduction in the rate of deterioration with riluzole: calculations questionable and clinical significance unclear; • Little evidence of difference in adverse event rates. **Conclusions:** *"There is strong clinical support for the use of riluzole in forms of MND other than ALS, but the current licensed indications limit its use to ALS alone. The inclusion criteria for the published clinical trials have been restricted to a diagnosis of the ALS form of MND alone."* *"Current estimates of the cost-effectiveness of riluzole must be viewed cautiously. Some of the key remaining uncertainties on benefits for the economic analysis concern the disease stage(s) in which survival gain is experienced, the quality of life utility weights for ALS health states and the mean gain in life expectancy for individuals who take riluzole. Estimates from the two fully published trials suggest a gain in median survival time of 2 months to 4 months. It is clear that riluzole is associated with a net increase in costs to the health service, although the magnitude of the increase is difficult to predict accurately."*
Bryan (2001)	**Update to Nice (2001) with additional data on longer term survival from one included trial:** • Lecomblez (1996) include survival data only to 18 months; • Since survival gain was a key parameter, economic analysis required extrapolation beyond the end of the trial, which did not provide equivalent data for placebo group or riluzole doses other than 100mg; • Additional unpublished data on survival at 48 months for 100 mg only) was provided to NICE and further analyses were performed.	**Revised analysis:** • Larger survival gain for patients on riluzole and a higher cost than originally estimated; • More attractive cost-effectiveness profile for riluzole. **Cautions:** • *"The data used in the analysis reported here are from a single trial (Lacomblez et al) and for the active drug include only patients allocated to the riluzole 100mg arm- all data on patients allocated to either 50mg or 100mg have been ignored. Long-term follow-up data on such patients have not been provided.* • *We still do not have comparative data beyond 18 months. The assumption made in this analysis is that patients allocated to placebo do not follow a similar path, beyond 18 months, to riluzole*

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
		patients. It remains the case that further research is required. In particular firmer estimates are required of the longer-term survival for patients in the absence of riluzole, possibly using data from observational cohort studies of the natural history of ALS, where available."

Table 5: Descriptive (hypothesis-generating) studies: organization of care for ALS

Citation	Objective/Methods	Results/Conclusions
Van der Steen (2009)	**To examine the costs of care at multidisciplinary ALS centers Vs general care:** • Academic medical center, Netherlands; • Cross-sectional: patients (grouped by type of treatment, disease characteristics) and caregivers interviewed and kept cost diaries for 6 months (2001-04); costs standardized to 2003; • Direct (paid by patient) and indirect costs (lost resources) considered.	**208 ALS patients and their carers:** • Mean monthly costs for ALS center group, €1336; general care group, €1271; **Conclusions:** *"This study shows that the costs of multidisciplinary ALS care were practically identical to the costs of general care. Earlier study* (Van den Berg, 2005; below) *showed that patients receiving multidisciplinary care had a better quality of life; therefore, the present study encourages the formation of multidisciplinary teams of professionals specialized in ALS care to further improve standards of care and QoL for patients suffering from ALS."*
Van den Berg (2005)	**To examine effects of multidisciplinary care on QoL in ALS:** • Academic medical center, Netherlands; • Cross-sectional: Patients and caregivers interviewed and completed SF-36; • Multidisciplinary teams: headed by consultant in rehab medicine with at least physical and occupational therapists, speech pathologist, dietition and social worker; used Dutch ALS consensus guideline; had at least 6 incident cases/yr.	**133 multidisciplinary care patients; 75 general care:** • Clinical characteristics/functional loss of two groups similar; • % with adequate aids/appliances higher in MD group: 93.1Vs 81.3; p = 0.008; number of visits to professional caregivers similar; • MD patients had better mental QoL on mental summary score; p = 0.01; • QoL differences most pronounced in domains of social functioning and mental health; NS differences in physical summary score, VAS, or caregiver QoL. **Conclusions:** *"High standard of care improves mental quality-of-life in patients with ALS."*
Rio (2007)	**Survey: nutritional advice by dietitions to ALS patients:** • UK and Canada: • Telephone interviews using standardized questionnaire.	**23 responses:** • 78% belong to multidisciplinary teams; • 22% had > 4 yrs experience with ALS/MND; • BWL and BMI used to assess nutritional status; equation for energy and protein need estimations differed; • Most frequent advice: high calorie; texture modification; prescription supplements; • RBB guidelines exist but use unclear; PEG discussed when patients became dysphagic, energy intake inadequate; weight loss 10%; or FVC reduced. **Conclusions:** *"Nutritional assessment techniques and dietary advice should be standardized. Dietetic collaboration at national and international level is recommended to reduce professional isolation. Training and support in ALS/MND nutrition should be made available as part of post-dietetic registration. Further dietetic research is required to stimulate nutritional care."*
Chiò (2006)	**Effects of tertiary centers for ALS on outcomes and use of hospital facilities:** • PARALS established1995: multicenter ALS registry for two Italian regions; • Patients entering registry1995-1996 and followed through	**97 patients followed by ALS centers; 124 by general neurology clinics:** • ALS centers: patients 4 yrs younger; received PEG and NIPPV more often; had longer median survival (1080 Vs 775 days) when stratified by age, site of onset; respiratory function at diagnosis; • General neurology clinics: more frequently admitted for acute events; and hospital stay shorter than ALS center patients (5.8 Vs 12.4 days).

Citation	Objective/Methods	Results/Conclusions
	2003; • Two operational ALS centers during that period, both with interdisciplinary teams; • Patients were seen approx every 8 weeks and symptoms managed according to best available evidence: PEG considered at weight loss > 10% or for episodes of choking; NIV when FVC< 50% of predicted or nocturnal oximetry showed marked desaturation; riluzole free from 1996 and offered to all patients; all visits and services free to patients; • Patients considered attending if followed for at least 2 months by one of the centers.	**Conclusions:** *"Improved survival was seen in patients attending tertiary ALS centers, independently from all other known prognostic factors, possibly through a better implementation of supportive treatments. Moreover, because of these centres, the hospitalization rate was markedly reduced, thus offering a cost-effective service to patients with ALS and to the community as a whole."*
Traynor (2003)	**Irish ALS Register:** • All ALS cases diagnosed in Ireland, 1996-2000; • Outcomes in patients at multidisciplinary ALS clinics Vs general neurology clinics; • ALS clinics: team of neurologist, specialist nurse; physical, occupational, speech therapist, pulmonologist; nutritionist; psychologist; social worker); patients reviewed every 6 weeks; all services no cost to patient; ALS team plus local hospice during terminal stage.	**82 patients at ALS clinic; 262 general neurology:** • ALS clinic patients averaged 5 yrs younger (60.1 Vs 65.6 yrs); more likely to receive riluzole (99 Vs. 61%); median survival 7.5 months longer (p<0.0001); 1 yr mortality decreased by 29.7%; and survival by 9months in bulbar onset; • Multivariate analysis: attendance at ALS clinic was independent predictor of survival (HR, 1.47; p = 0.02). **Conclusions:** *"ALS patients who received their care at a multidisciplinary clinic had a better prognosis than patients attending a general neurology clinic. The data suggest that active and aggressive management enhances survival, particularly among ALS patients with bulbar dysfunction. The effect of clinic type must be considered in future clinical trials design."*
Borasio (2001)	**Survey of palliative care practice among member of European ALS Study Group:** • 110 members in18 countries (Italy, Germany, UK, France Sweden, Denmark, Belgium, Greece, Poland, Spain, Finland, Hungary, Ireland, Israel, Netherlands, Norway, Portugal, Yugoslavia) including all major ALS centers in Europe; • 111-item survey covering: giving diagnosis; symptomatic treatment; nutrition/PEG; community services; respiratory support; terminal care.	**73 completed surveys returned:** • Response rate 66%; • Centers follow average of 74 patients (10-500); • Average 40 new patients/yr (5-200); • mean FU interval 11 weeks; • most centers participate in drug trials: mean past trials, 1.5 (0-8); • **Areas of consensus:** presenting diagnosis to patient plus relative (85%); offering short term FU (90%); regular weight checks (82%); availability of PEG (94%); discussion of respiratory issues (90%); • **Main differences:** symptomatic drug treatments; availability of services; ventilation terminal care; • "Considerable" interest in palliative care trials. **Conclusions:** *"Great efforts are made by the centers to offer the best possible palliative care to ALS patients. The discrepancies in the type of care offered might be resolved by adopting a common standard, on the basis of available evidence and mutual consensus. Several areas of ALS patient care would benefit from controlled studies to establish an evidence base for treatment decisions."*

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VA TECHNOLOGY ASSESSMENT PROGRAM

Mission Statement

To enhance the health of Veterans and the nation by providing and fostering technology assessment for evidence-based health care

Values

Integrity and pride in the work that we do

Quality products that are clinically valid and methodologically transparent

Objectivity in evaluating and presenting research evidence

Commitment to continuous quality improvement and to the guiding principles of evidence based practices

Flexibility in responding to changes in VA and the larger healthcare environment

Innovation in designing products and their dissemination to best meet VA's needs

Accessibility of products and services